NTP
National Toxicology Program

Draft NTP Monograph on Health Effects of Low-level Lead

Andrew A. Rooney, Ph.D.

Office of Health Assessment and Translation

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Introduction

Lead (Pb) exposure remains a significant health concern despite policies and practices that have resulted in continued progress toward reducing exposure and lowering blood Pb levels in the U.S. population.

Nomination and Scope of the Evaluation

- NIOSH nominated Pb for evaluation
- NTP focused the evaluation on epidemiological data for health effects at blood lead levels <10μg/dL
  - Health effects are well established at higher levels
  - CDC's definition of elevated blood lead is ≥10μg/dL for all ages
- NTP expanded the scope to include:
  - Neurological effects
  - Immune effects
  - Cardiovascular effects
  - Renal effects
  - Reproductive and developmental effects

Key Questions

What is the evidence that adverse health effects are associated with blood Pb levels <10μg/dL?

- What neurological, immune, cardiovascular, renal, reproductive, and developmental effect(s) are associated with blood Pb levels <10μg/dL?
- What is the blood Pb level associated with the health effect (i.e., <10μg/dL or <5μg/dL)?
- At which life stage (childhood or adulthood) is the effect identified?
- Are there data to evaluate the association between bone Pb and the health effect and how does the association to this biomarker of Pb exposure compare to the association with blood Pb?

Organization of the Monograph

- Executive Summary
- Methods
- Exposure
- Health Effects Sections
  - Neurological Effects
  - Immune Effects
  - Cardiovascular Effects
  - Renal Effects
  - Reproductive and Developmental Effects

Approach to Develop Health Effects Conclusions

- NTP Considered four possible conclusions for specific health effects in each area:
  - **Sufficient Evidence of an Association**
  - **Limited Evidence of an Association**
  - **Inadequate Evidence of an Association**
  - **Evidence of No Association**

NTP Considered Four Possible Conclusions

- **Sufficient Evidence of an Association**:
  a relationship is observed between the exposure and health outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence
- **Limited Evidence of an Association**
- **Inadequate Evidence of an Association**
- **Evidence of No Association**

NTP Considered Four Possible Conclusions

- **Sufficient Evidence of an Association**
- **Limited Evidence of an Association**:
  an association is observed between the exposure and health outcome for which a causal interpretation is credible, but chance, bias, and confounding could not be ruled out with reasonable confidence
- **Inadequate Evidence of an Association**
- **Evidence of No Association**

NTP Considered Four Possible Conclusions

- **Sufficient Evidence of an Association**
- **Limited Evidence of an Association**
- **Inadequate Evidence of an Association**: the available studies are insufficient in quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association between exposure and health outcome, or no data in humans are available
- **Evidence of No Association**

NTP Considered Four Possible Conclusions

- **Sufficient Evidence of an Association**
- **Limited Evidence of an Association**
- **Inadequate Evidence of an Association**

- **Evidence of No Association:** there are several adequate studies covering the full range of levels of exposure that humans are known to encounter (in this case limited to blood Pb levels <10µg/dL), which are mutually consistent in not showing an association between exposure to the agent and any studied endpoint

Basis for Conclusions

- **Primary literature** - epidemiological studies with mean blood Pb levels <10μg/dL
  - Consideration of study design
- **Supported by**
  - Bone Pb data
  - Laboratory animal data
  - Authoritative sources
    - US EPA 2006 Air Quality Criteria Document for Lead
    - ATSDR 2007 Toxicological Profile for Lead
    - Technical advisors

Organization

- Health effects sections begin with a statement of the NTP's conclusion on whether or not the effect is associated with blood Pb <10μg/dL or <5μg/dL
  - Age at which it is identified
  - Timing of exposure associated with the effect
- Key data and the principal studies considered in developing NTP's conclusions are discussed in detail

Organization

- Human studies considered in developing conclusions were abstracted into appendices

- The health effects sections end with summary of:
  - Basis for the NTP's conclusions
  - Experimental animal data
  - Consistency with previous EPA and ATSDR reports
    - US EPA 2006 Air Quality Criteria Document for Lead
    - ATSDR 2007 Toxicological Profile for Lead

What does it mean to refer to blood Pb <10μg/dL?

- Blood Pb reflects an equilibrium between current environmental Pb exposure and the body burden of Pb
- **Blood Pb**
  - Reflects current exposure
  - Widely available exposure metric
- **Bone Pb**
  - Reflects cumulative exposure
  - Bone stores 70 – 95% of total body burden
  - Data are not widely available

Blood Pb <10μg/dL

- Environmental Pb levels were higher in the US prior to bans on Pb in paint, solder, and gasoline
- Childhood blood Pb decreased 10-fold over 30 years
  - 1976-1980 mean blood Pb = 15.1μg/dL
  - 2007-2008 mean blood Pb = 1.51μg/dL
- Health effects in adults today may have been influenced by blood Pb levels >10μg/dL earlier in life

Blood Pb <10μg/dL

- Multiple studies report significant associations between concurrent blood Pb levels <10μg/dL and health effects in adults
- The association with blood Pb is supported by:
  - Consistency of effects across epidemiological studies
  - Coherence with animal data
- It is well recognized that the role of early-life Pb exposure cannot be discriminated from the role of concurrent blood Pb in adults without additional long term studies

Organization of the Review

- Executive Summary
- Methods
- **Exposure**
- **Health Effects Sections**
  - **Immune Effects**
  - **Cardiovascular Effects**
  - **Reproductive and Developmental Effects**
  - **Renal Effects**
  - **Neurological Effects**


National Toxicology Program

DRAFT NTP MONOGRAPH ON HEALTH EFFECTS OF LOW-LEVEL LEAD

Charge

The Peer-Review Panel is charged to:

1) To determine whether the scientific information cited in the draft monograph is technically correct, clearly stated, and objectively presented and

2) To determine whether the scientific evidence presented in the draft monograph supports the NTP's conclusions regarding health effects of low-level Pb